American Journal of Medical Genetics 61:178–181 (1996)

# SHORT Syndrome: A New Case With Probable Autosomal Dominant Inheritance

**Giovanni Sorge, Martino Ruggieri, Agata Polizzi, Antonino Scuderi, and Massimo Di Pietro**
*Departments of Pediatrics (G.S., M.R., A.P.) and Ophthalmology (A.S., M.D.P.), University of Catania, Catania, Italy*

**A further case of SHORT syndrome is reported. This 9-year-old Italian boy was short of stature and had partial lipodystrophy, minor facial anomalies, mild hyperextensibility of joints, ocular depression, Rieger anomaly, delay in speech development and in dental eruption. The father and sister showed a striking similarity to the propositus. Moreover, the sister had bilateral and symmetrical lens opacities, which have not been reported previously in affected subjects or their relatives. A variable expression of an autosomal dominant gene can be considered in the present family.**


**KEY WORDS: SHORT syndrome, Rieger anomaly, short stature, multiple abnormalities, lens opacities, autosomal dominant inheritance**

## INTRODUCTION

SHORT syndrome was first described by Gorlin et al. [1975], and Sensenbrenner et al. [1975]. The main clinical manifestations, short stature, hyperextensibility of joints and/or inguinal hernia, ocular "depression," Rieger anomaly and delay of dental eruption are summarized in the acronym SHORT [Gorlin et al., 1975]. Other consistent findings are slow weight gain, frequent illness during infancy, distinct facial abnormalities, and partial lipodystrophy [Gorlin et al., 1990]. To our knowledge, 7 cases of SHORT syndrome have been reported [Schwingshandl et al., 1993]. We report on the first Italian patient affected with this condition.

## CLINICAL REPORT

The propositus, a 9-year-old boy, is the first born to nonconsanguineous Italian parents. He was the term product of an uneventful pregnancy. Birth weight was 3,800 g (50th centile), birth length 50 cm (40th centile), and occipitofrontal head circumference (OFC) at 1 month was 36 cm (50th centile). Initial weight gain was slow falling below the 3rd centile at 10 months. During infancy and childhood he was hospitalized several times for failure to thrive and recurrent tonsillitis. Dental eruption was delayed, with his first tooth erupting at 14 months. Psychomotor development was normal: he sat at 6 months, stood at 10 months, and walked at 14 months. Speech development was delayed (36 months).

At 7 years, he was first referred in fair general condition. Weight was 14 kg (<3rd centile), height 103 cm (3rd centile) and OFC 51 cm (25th centile). He was very slim and had a "triangular face," broad forehead, deeply set eyes, bushy eyebrows, horizontal palpebral fissures, broad nasal bridge, hypoplastic alae with short and triangular columella; short and flat philtrum, small mouth with highly arched palate and hypoplastic mandible (Fig. 1). Ears were low-set and apparently anteverted with hypoplastic helix and tragus. Teeth were small and stained. The voice was high-pitched. There was mild hyperextensibility of joints. Subcutaneous tissue was poorly represented, mostly on upper limbs. He had finger-like thumbs with long and thin fingers, clinodactyly of right 5th finger and partial cutaneous syndactyly between 2nd, 3rd and 4th fingers. Feet were long with broad hallux. There were neither café-au-lait spots nor body asymmetry. Heart was normal. The other physical findings and neurologic status were normal. Currently, at age 9, he attends normal school where he manages appropriately for his age. He has a shy and introverted personality. Results of routine blood and urine analyses, extensive endocrinological investigations including growth hormone levels after stimulation, thyroid function studies, somatomedins, oral glucose tolerance tests and other biochemical investigations were normal. Banded high resolution chromosomes were normal. Ophthalmologic examination demonstrated relatively large corneae: corneal diameter was $12.5 \times 13$ (normal $11.5 \pm 0.5$). Slit lamp and gonioscopic examination showed anterior displacement and thickening of Schwalbe ring with trabecular iridocorneal adhesion which are typical manifestations of Rieger anomaly. Intraocular pressure and fundi were

Received for publication December 14, 1994; revision received July 6, 1995.

Address reprint requests to Giovanni Sorge, M.D., Clinica Pediatrica 1ª, Università di Catania, Viale Andrea Doria 6, 95125 Catania, Italy.

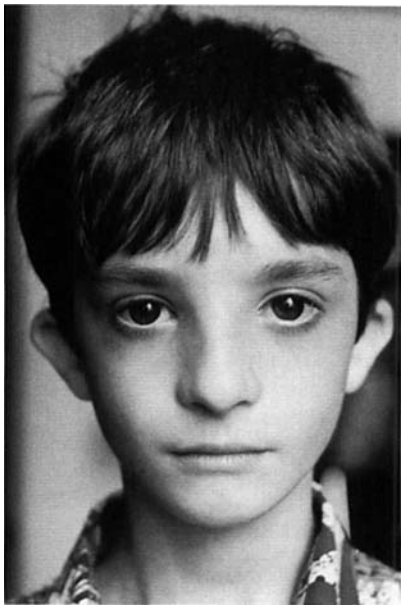

Fig. 1. The propositus, age 7 years. Note "triangular" face, broad nasal bridge with hypoplastic alae, and small mouth.

normal. Results of cardiac, abdominal and pelvic ultrasonographic studies, as well as audiometric examination were normal. Cerebral MRI showed hyperintense areas on T2-weighted images localized in the periventricular parietal regions of both hemispheres. Bone age at 7$^{7}/_{12}$ years was 6 years. Thus, he had nearly all of the manifestations characteristic of previously described patients with SHORT syndrome (Table I).

The father of the propositus, a 40-year-old man, had an appearance strikingly similar to that of his son (Fig. 2). The eyes were deeply set with marked frontal prominence; the ears were large and prominent with hypoplastic helix and tragus but normally positioned; he had pronounced loss of facial and body fat, especially over trunk and limbs, without lipoatrophy of the buttocks; his weight was 38 kg and height 156 cm (<3rd centile). Eye examination showed mild myopia. Slit lamp and gonioscopic examination evinced no other ocular abnormalities. Dental eruption was known to be delayed, with his first tooth erupting at 10 months. He had full dental prostheses. Results of routine blood and urine tests were normal as well as fasting blood sugar.

The sister of the propositus was the term product of an uneventful pregnancy. This 11-year-old girl had an appearance similar to that of her brother (Fig. 3). Dental eruption had been delayed up to 11 months. She had hypermetropia and slit lamp and gonioscopic examination showed round to oval bilateral and symmetrical lens opacities. No other relative had facial or ocular anomalies. Father's relatives had an average height on the 10th centile.

TABLE I. Comparison of Findings in SHORT Syndrome*, in the Condition Described by Aarskog et al. [1983], and in Present Patient

| Findings | SHORT syndrome | Aarskog et al. [1983] | Present case |
|---|---|---|---|
| Sex | M and F | M | M |
| IUGR (intrauterine growth retardation) | + | + | + |
| Slow weight gain | + | + | + |
| Frequent illness | + | − | + |
| Triangular face | + | + | + |
| Anteverted ears | + | + | + |
| Telecanthus | ± | − | − |
| Deeply set eyes | + | + | + |
| Rieger anomaly | + | + | + |
| Wide nasal bridge | + | − | + |
| Hypoplastic alae | + | + | + |
| Delayed dental eruption | + | + | + |
| Chin dimple | ± | − | − |
| Micrognathia | + | + | + |
| Clinodactyly | ± | − | + |
| Lack of subcutaneous fat: | | | |
| Face | + | + | + |
| Trunk and limbs | + | − | + |
| Buttocks | − | + | − |
| Hypotrichosis | − | + | − |
| Hypospadia | − | + | − |
| Joint hyperextensibility | + | − | + |
| Short stature | + | + | + |
| Hearing loss | ± | − | + |
| Functional heart murmur | ± | + | − |
| Inguinal hernia | ± | + | − |
| Delayed bone age | + | + | + |
| Delayed speech | + | + | + |
| Normal intellect | + | + | + |
| Glucose intolerance | − | + | − |
| Insulinopenic diabetes | − | + | − |

*Gorlin et al. [1975]; Sensenbrenner et al. [1975]; Toriello et al. [1985]; Lipson et al. [1989]; Schwingshandl et al. [1993].

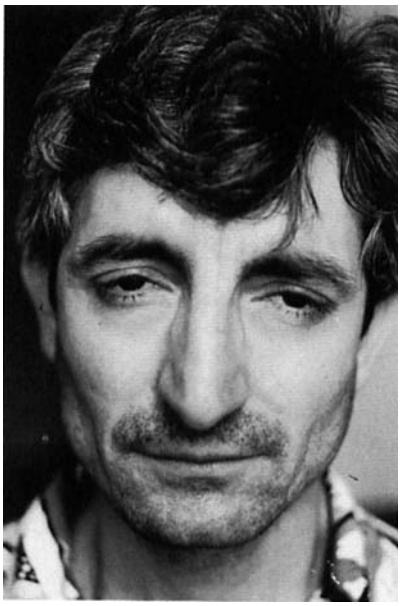

Fig. 2. Father of the propositus at 40 years. Note the deeply set eyes, the large ears, and the scarce facial fat.

## DISCUSSION

This boy has striking similarities to the original cases of Gorlin et al. [1975] and Sensenbrenner et al. [1975] and even more to the case of Toriello et al. [1985]. Although our patient did not show full expression of Rieger anomaly [McKusick, 1992], nevertheless he had the typical iridocorneal anomalies of iridogoniodysgenesis [Brooks et al., 1989; Geyer et al., 1994]. Therefore, we think that his phenotype is consistent with the diagnosis of SHORT syndrome. Heart murmur, hernia or sensorineural deafness, reported in some previous cases [Gorlin et al., 1975; Sensenbrenner et al., 1975; Toriello et al., 1985], are not present in this patient. Nevertheless he shares almost all the other physical findings referred to in the previous clinical reports [Schwingshandl et al., 1993], as shown in Table I.

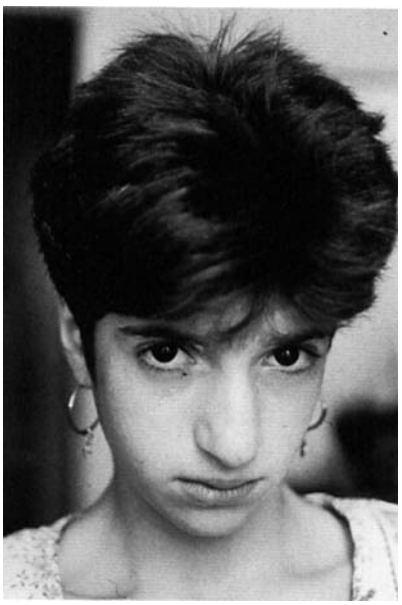

Fig. 3. Sister of the propositus at 11 years. Similar phenotype as brother and father.

We ruled out Johanson-Blizzard syndrome [Jones, 1988], because of normal thyroid function and normal intellect; the Silver-Russell syndrome [Jones, 1988] because of the normal birth weight and OFC, and lack of other physical findings; the neonatal progeroid syndrome [Wiedemann et al., 1982] because of normal mental development and differences in physical findings.

Iridocorneal abnormalities in combination with short stature, delayed osseous maturation and developmental delay has been reported by Stratton et al. [1989], but those patients, a brother and sister, also had congenital dislocation of the hip, high umbilicus, minor foot anomalies and congenital glaucoma, lacking triangular face and lipoatrophy.

Aarskog et al. [1983] described what seems to be a similar and dominantly inherited disorder in four individuals in 3 generations. All had Rieger anomaly. Two members manifested diabetes mellitus at 14 and 39 years, respectively, and another, glucose intolerance at 55 years. The lipodystrophy was present from infancy and affected not only the face but the buttocks, without progression. Additional findings included midface hypoplasia, retarded bone age, hypospadias, and hypotrichosis. Complete and pronounced lipoatrophy of the upper limbs and joint hyperextensibility, together with lack of fat atrophy on the buttocks and hypotrichosis in all the members of the present family, and hypospadias in male patients, led us to distinguish our patients from Aarskog et al.'s cases [1983]. Retarded bone age, which was found in our propositus, is a manifestation shared by both conditions of SHORT and the syndrome described by Aarskog et al. [1983]. Glucose intolerance or diabetes mellitus were not present in the propositus or in the affected members of his family, although diabetes may still develop in this case. Diabetes mellitus secondary to severe insulin resistance has been described as additional manifestation of SHORT syndrome in one case [Schwingshandl et al., 1993]. In Table I is reported a comparison between SHORT syndrome, the syndrome reported by Aarskog et al. [1983] and our patient.

The father and the sister of our propositus showed a strikingly similar appearance to that of the propositus: in fact they showed deeply set eyes with marked frontal prominence and large prominent ears with hypoplastic helix and tragus. The father showed loss of facial fat, scarcely present subcutaneous fat and height and weight below the third centile. The sister had bilateral and symmetrical lens opacities that have never been previously reported in SHORT syndrome. As the anterior chamber development is induced by the lens, once the latter is established, during early eye developmental stages [Moore, 1988], one can argue that both anomalies, i.e., Rieger anomaly and lens opacities, might be part of the same defect in SHORT syndrome.

When looking at the dominant mode of transmission shown by present family, it should be likely that our pa-

tients have the condition described by Aarskog et al. [1983], which is dominantly inherited, rather than SHORT syndrome, which seems to be inherited as an autosomal recessive trait. Actually, the mode of inheritance of SHORT syndrome remains uncertain and there is some confusion in the literature due to the fact that a clear distinction between SHORT syndrome, and the similar syndrome described by Aarskog et al. [1983], has not been always made. In McKusick catalog [1992] these two conditions are reported separately, one inherited as autosomal recessive, the classical SHORT syndrome (MIM 269880), and the other as autosomal dominant, the syndrome described by Aarskog et al. [1983] (MIM 151680). Such assumption does not seem to be universally accepted. Lipson et al. [1989] and more recently Schwingshandl et al. [1993] lump the condition described by Aarskog et al. [1983] into the same category as the patients described by Gorlin et al. [1975], Sensenbrenner et al. [1975] and Toriello et al. [1985], suggested that explanations other than autosomal recessive inheritance might be considered in SHORT syndrome, such as variable expression or germinal mosaicism for an autosomal dominant gene [Lipson et al., 1989], with some cases of SHORT syndrome representing variants of the syndrome described by Aarskog et al. [Lipson et al., 1989]. Moreover, we know from the literature [Stratton et al., 1989] that R.J. Jorgeson in 1987 observed an unreported family with SHORT syndrome in at least two generations.

If we do accept the distinction proposed by McKusick [1992], our family should be considered as a variant of the syndrome described by Aarskog et al. [1983], because our patients lack lipodystrophy in limited areas of buttocks, glucose intolerance, insulinopenic diabetes, hypospadia and hypotrichosis, that are major manifestations of this syndrome. On the other hand, the absence of the above mentioned clinical traits and the presence of triangular face and upper limbs lipoatrophy seem to strongly suggest a diagnosis of classical SHORT syndrome although inherited as an autosomal dominant trait.

In conclusion, we think that only the description of further patients falling within the spectrum of the above syndromes will permit the establishment of a clearer nosology.

## REFERENCES


Aarskog D, Ose L, Pande H, Eide N (1983): Autosomal dominant partial lipodystrophy associated with Rieger anomaly, short stature, and insulinopenic diabetes. Am J Med Genet 15:29–38.

Brooks JK, Coccaro PJ, Zarbin MA Jr (1989): The Rieger anomaly concomitant with multiple dental, craniofacial, and somatic midline anomalies and short stature. Oral Surg 68:717–724.

Geyer O, Loewenstein A, Garty BZ, Lazar M (1994): Different manifestations of Rieger syndrome in monozygotic twins. J Pediatr Ophthalmol Strabismus 31:57–58.

Gorlin RJ, Cervenka J, Moller K, Horrobin M, Witkop J (1975): Rieger anomaly and growth retardation (the S-H-O-R-T syndrome). In Bergsma D (ed): "Malformation Syndromes." New York: Excerpta Medica for the National Foundation. March of Dimes. BD:OAS XI(2):46–48.

Gorlin RJ, Cohen MM Jr, Levin LS (1990): "Syndromes of the Head and Neck." 3rd ed. Oxford: Oxford University Press.

Jones KL (1988): "Smith's Recognizable Patterns of Human Malformation." 4th ed. Philadelphia: W.B. Saunders Co.

Lipson AH, Cowell C, Gorlin RJ (1989). The SHORT syndrome: Further delineation and natural history. J Med Genet 26:473–475.

McKusick VA (1992): "Mendelian Inheritance in Man. Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes." 11th ed. Baltimore: Johns Hopkins University Press.

Moore KL (1988): "The Developing Human. Clinically Oriented Embryology." 4th ed. Philadelphia: W.B. Saunders Co.

Schwingshandl J, Mache CJ, Rath K, Borkenstein MH (1993): SHORT syndrome and insulin resistance. Am J Med Genet 47:907–909.

Sensenbrenner JA, Hussels IE, Levin LS (1975): CC—a low birthweight syndrome, Rieger anomaly. In Bergsma D (ed): "Malformation Syndromes." New York: Excerpta Medica for the National Foundation. March of Dimes. BD:OAS XI(2):423–426.

Stratton RF, Parker MW, McKeown A, Johnson CP (1989): Sibs with growth deficiency, delayed bone age, congenital hip dislocation, and iridocorneal abnormalities with glaucoma. Am J Med Genet 32:330–332.

Toriello HV, Wakefield S, Komar K, Higgins JV, Waterman DF (1985): Report of a case and further delineation of the SHORT syndrome. Am J Med Genet 22:311–314.

Wiedemann HR, Grosse FR, Dibbern H (1982): Angeborenes pseudohydrozephales Progeroid-Syndrom. In "Das Charakteristische Syndrom." Stuttgart: E.K. Schautter Verlag, pp 196–197.